Editorial

Diabetes and coronary artery disease: time to stop taking the tablets?

Patients with diabetes develop accelerated coronary artery disease and are 10 to 20 times overrepresented among those suffering from acute myocardial infarction.[1 2] Mortality in the year following infarction is up to twice that of non-diabetics, and coronary artery disease remains the most common single cause of death in diabetic patients.[3]

Despite the wide prevalence of diabetes and its high rate of coronary artery disease, it remains unclear how diabetic patients with this complication should best be treated. An emerging concern is that standard treatments for the million or so non-insulin dependent diabetic patients in the UK may be contributing to the considerable morbidity and mortality from cardiovascular disease. These patients are most commonly treated with oral hypoglycaemic agents, usually sulphonylureas. Concern about such treatment, particularly sulphonylureas, has been expressed intermittently for nearly 30 years.[4–7] Such concerns have become increasingly focused recently because of improved understanding of the molecular mechanisms of action of sulphonylureas, accumulating evidence of the superiority of insulin in treating diabetic patients following acute myocardial infarction,[8] the clinical availability of potassium channel opening agents, and reminders of the hazards of biguanide treatment.

During conditions of low intracellular ATP concentration, including ischaemia, an ATP sensitive potassium (K_{ATP}) channel opens in the cell membrane of myocardial and arterial smooth muscle cells. This results in reduced myocardial contractility and increased arterial vasodilatation. Pancreatic β cells also contain K_{ATP} channels and the hypoglycaemic action of sulphonylureas is dependent on K_{ATP} channel closure: indeed these agents are regarded as prototypical antagonists. In animal studies sulphonylureas cause coronary vasoconstriction with consequent myocardial ischaemia, and opening K_{ATP} channels pharmacologically has been shown in many models to confer protection during myocardial ischaemia.[5] Such benefit probably derives, at least in part, from reducing contractility and increasing blood flow, thereby limiting myocardial energy expenditure, increasing substrate delivery, and promoting metabolite removal. In clinical practice, such potential benefit is reflected by the efficacy of potassium channel openers such as nicorandil in treating symptomatic coronary artery disease.

Potentially more intriguing is the possibility that K_{ATP} channels play a pivotal role in the endogenous adaptation known as "ischaemic preconditioning".[9] This is arguably the most powerful intervention available to limit the effects of experimental myocardial ischaemia,[10] with beneficial effects on infarct size if subsequent reperfusion takes place, and on arrhythmias.[11] There is considerable circumstantial evidence that such adaptation occurs in man, as it does in all species studied to date.[12] Such evidence as exists in man suggests that where such protective adaptation occurs, it can be blocked by sulphonylureas both in vitro and in vivo.[13 14] The concentrations of sulphonylureas required to activate cardiac and vascular channels may be between 100 and 1000 times higher than those required to induce pancreatic insulin release, so it is arguable that these effects are not pathophysiologically relevant. However, K_{ATP} channel blockade in preconditioning studies almost always proves deleterious, and there are no reports of a beneficial effect.[5 6] Sulphonylurea treatment may therefore not only block preconditioning, but theoretically also impede other early responses to ischaemia such as coronary artery vasodilatation and recruitment of coronary collaterals.

If sulphonylureas are detrimental in experimental myocardial ischaemia then insulin treatment in the setting of clinical acute myocardial infarction might be superior to sulphonylureas in at least five ways. It would promote better control of blood glucose, may have an intrinsic protective effect,[15] may mimic a protective effect of insulin-like growth factors,[16] may reduce the harmful effects of non-esterified fatty acids,[17] and, as discussed above, could permit endogenous protective mechanisms to limit myocardial damage. Such theoretical possibilities appear to be mirrored by benefits in clinical practice, the most notable data being from the diabetes insulin-glucose in acute myocardial infarction (DIGAMI) trial,[8] in which diabetic patients with acute myocardial infarction were treated acutely with a glucose-insulin infusion, and subsequently with subcutaneous insulin. Although no short term benefit was evident, the trial showed a reduction from 44% (control) to 33% (insulin treatment) in all cause mortality during the mean 3.4 year follow up period. The control group was given a variety of treatments so it was not possible to draw conclusions specifically about sulphonylurea treatment. Nonetheless, this study gives unequivocal support for the notion of using insulin to treat diabetic patients with acute myocardial infarction. The benefits were most evident in those patients not taking insulin beforehand, a group who were thought to be at low cardiovascular risk. Re-examination of older work in the light of these findings has been revealing. Attention has focused once again on the university group diabetes program (UGDP) study,[4] which showed a worse natural history of infarction in diabetic patients treated with tolbutamide compared with other standard treatments including diet alone. Although significant criticisms were levelled both at the trial design and at certain statistical inferences drawn from it,[18] the implications of this study have been minimised over the last generation, possibly because "of a lack of a plausible mechanism for the...results".[7] Two smaller studies have concurred with these findings, although other small studies have shown conflicting results.[6] A definitive trial is required to investigate this important question, but it is intriguing to speculate that the swing away from sulphonylurea treatment in the United States following the UGDP study has generated clinical data which may already hold some of the answers.

In experimental settings, some sulphonylureas, particularly second generation agents, have been shown to have potentially beneficial effects, for instance on lipid profile, on clotting, and on early arrhythmias in acute myocardial infarction.[5 6] The argument has yet to be made that these actions are likely to be transposed into concrete clinical benefit. The relative importance of such effects compared with a potentially deleterious effect, or with risks from

insulin treatment, can only be evaluated by a well designed trial comparing outcome in patients with type II diabetes treated with sulphonylureas, other oral agents, insulin, or diet alone. The hypothesis that needs addressing is that cardiovascular events are more common in patients treated with sulphonylureas, and that the prognosis following acute myocardial infarction is worse in these patients. If the K_{ATP} channel hypothesis is correct then adding a potassium channel opener to insulin treatment in the setting of acute myocardial infarction should have an additional measurable clinical benefit. This also remains to be tested in clinical practice and would form a logical and valuable extension of the information provided by the DIGAMI trial.

What of biguanide treatment? Metformin, the only biguanide available clinically in the United Kingdom, is often used as first line treatment in obese diabetic patients. It has a distinct molecular action to sulphonylureas and does not carry any of the adverse consequences of potassium channel closure. A serious potential hazard is that it can cause type B lactic acidosis in settings where intravascular radiographic contrast media are used, such as coronary angiography or angioplasty. This complication develops only on a background of reduced renal function, so diabetic patients may be at increased risk as many show a degree of impaired renal function. This may not be universally appreciated by invasive cardiologists, but current Royal College of Radiology guidelines (BFCR(96)8) recommend avoiding metformin for 48 hours before and after such a procedure. This begs the question of whether patients likely to need such procedures would also be better served by being on chronic insulin treatment.

If insulin were shown to offer clear advantages over other hypoglycaemic treatments in diabetes this would have major public health implications. The wholesale conversion to insulin of patients currently taking oral hypoglycaemic agents would be a huge undertaking in terms of patient tuition and acceptance, blood glucose monitoring, and cost. These issues also require formal address to confirm whether a potentially desirable change in clinical practice can be shown to be feasible and cost-effective. It would be important to determine whether all diabetics would benefit from insulin, or whether instituting insulin treatment at the time of a first cardiovascular event was a more effective strategy. Clinical trials to answer these questions would require sufficient statistical power to detect what may be small absolute differences in outcome, but which might nonetheless be important on a population scale. There are striking parallels with the debate about the value of thrombolytic treatment in myocardial infarction during the 1970s and early 1980s. Again, good theoretical and experimental reasons for recommending profound changes in clinical practice were dogged by conflicting outcomes from relatively small trials, and only the "mega-trials" performed subsequently established the place of such treatment beyond doubt.

On current theoretical and clinical evidence we suggest that patients with diabetes and established coronary artery disease should all be treated during the acute phase of a myocardial infarct with insulin, and that insulin treatment should be continued indefinitely thereafter. More speculatively, sulphonylureas should not be given to diabetic patients with coronary disease. Biguanides should be avoided in patients likely to need procedures involving large volumes of radiological contrast media. It would also seem logical to highlight the potential physiological antagonism of potassium channel openers and sulphonylureas to prescribers, as this information is not currently contained in the *British National Formulary*.

The time to stop taking the tablets is, therefore, not yet—largely because sufficient clinical evidence is not available to support theoretical predictions of the superiority of insulin treatment in diabetic patients with coronary artery disease. However, given the large burden of morbidity and mortality that results from the combination of coronary artery disease and diabetes, the time has surely come to implement trials capable of answering this important economic and public health question, and to show whether current treatments for diabetes continue to fulfil the physician's first duty—to do no harm.

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